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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/818,875	03/27/2001	Eric B. Kmiec	Napro-4	2466

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EXAMINER	
ANGELL, JON E	
ART UNIT	**PAPER NUMBER**
1635	24

DATE MAILED: 05/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/818,875	KMIEC ET AL.	
	Examiner	Art Unit	
	J. Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *25-38 and 40-77* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *25-38 40-77* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. This Action is in response to the communication filed on 3/12/03, as Paper No. 23. The amendment has been entered. Claims 25 and 75 have been amended. Claims 25-38 and 40-77 are currently pending in the application and are examined herein.

2. Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

Continued Examination Under 37 CFR 1.114

3. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/12/03 has been entered.

Specification

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. For example, see page11, lines 14-15 and lines 23-25. All embedded hyperlinks must be removed from the specification in reply to this Action.

Claim Objections

5. Claim 50 is objected to because of the following informalities: claim 50 depends on claim 25 (through claims 40, 44, 45 and 49). Claim 25 clearly indicates that the cultured or selectively enriched cells are not human stem cells. However, claim 50 indicates that the cell can be one of several species, including a stem. It is respectfully pointed out that a stem cell encompasses all stem cells, including human embryonic stem cells. Therefore claim 50 is objected to because the species "stem cell" of claim 50 encompasses human stem cells--which does not further limit claim 25. Appropriate correction is required.

6. Claim 55 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Specifically, claim 55 depends on claim 25, which limits the oligonucleotide to 17-121 nucleotides in length. However, claim 55 indicates that the oligonucleotide of 25 is no more than 121 nucleotides in length. Therefore, claim 55 does not further limit claim 25. Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 35-38, 40-49 and 57-58 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

9. Claims 35-37 recites the limitation "said cellular proteins". There is insufficient antecedent basis for this limitation in the claim because claim 25 recites, "cellular repair proteins". Claim 38 depends on claim 37 and is rejected for the same reason.

10. Claim 40 recites the limitation "said protein". There is insufficient antecedent basis for this limitation in the claim because claim 25 recites, "cellular repair proteins". Claims 41-52 are dependent claims and are rejected for the same reason.

11. Claim 47 recites the limitation "said yeast". There is insufficient antecedent basis for this limitation in the claim because claim 46 recites "a yeast cell".

12. Claims 57 and 58 recite the limitation "said internally unduplexed deoxyribonucleotides domain". There is insufficient antecedent basis for this limitation in the claim because claim 25 recites, "oligonucleotide having a domain of at least 8 contiguous deoxyribonucleotides".

Appropriate correction is required.

Claim Rejections - 35 USC § 112, first paragraph

13. Claims 25-38, 40, 44, 45 and 49-77 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method of targeted sequence alteration of a nucleic acid present in a cell in culture or in a cell-free extract; as set forth in claim 26.

does not reasonably provide enablement for the full scope encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Specifically, the claims are not enabled for a method of targeted sequence alteration of a nucleic acid present in a cell in vivo, which is encompassed by the claim because the limitation "within selectively enriched cells" does not explicitly limit the claim to cells in culture (i.e. in vitro).

It is acknowledged that during an interview with Applicants representatives that agreement was reached regarding the present claim language with respect to 35 USC 112, first issues. However, upon further consideration the Examiner considers "selectively enriched cells" to encompass cells in vivo. It is believed that applicants were agreeable to limit the claim to cells in culture/in vitro (or a cell-free extract). It is pointed out that limiting the claim to a method using a cell in culture/in vitro would obviate the rejection pertaining to the method in a cell in vivo.

It is also pointed out that claim 26 and 50 encompasses making a targeted nucleic acid alteration in a stem cell, and claim 72 encompasses making a targeted nucleic acid alteration in a human hematopoietic stem cell. The only contemplated use for making genetic alterations in stem cells (and hematopoietic stem cells) is for stem cell therapy. However, the claims are not enabled for stem cell therapy for the reasons set forth below.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

The nature of the invention

The instant claims are drawn to a method for targeted sequence alteration of a nucleic acid using oligonucleotides, and encompass altering genetic material for the treatment of disease. Therefore the nature of the invention is a method of gene therapy, specifically, therapeutic gene targeting. Furthermore, the claims encompass making genetic alterations in stem cells for the purpose of stem cell therapy.

The breadth of the claims

The claims encompass making genetic alterations in target nucleic acid sequences (such as genes or gene regulatory elements) wherein the target nucleic acid sequences are present in cells *in vitro* and *in vivo*, as well as target nucleic acids in a cell free environment. Furthermore, the claims encompass using the method to make corrective alterations of mutant target sequences (i.e. therapeutic gene targeting). Regarding therapeutic gene targeting, the claims encompass making genetic alterations in cells that are in vitro and then transplanting the cells back into the subject (i.e. ex vivo therapy), as well as in vivo therapy which encompasses making genetic alterations by delivering the therapeutic oligonucleotide to a target cell in vivo (i.e. administering the oligonucleotide to a subject, and encompasses systemic administration). The claims also

encompass producing any type of genetic alteration, such as base substitution, and addition/deletion of any number of bases.

The unpredictability of the art and the state of the prior art

At the time of filing, the relevant art considered gene therapy as a whole to be unpredictable as efficient modes of delivering therapeutic nucleic acid to target cells had not been developed. Currently, the state of the art of gene therapy is still in its infancy as the art is plagued by unpredictability. For instance, Crystal (Science, 1995; 270:404-409) teaches that all of the human gene therapy studies have been plagued by inconsistent results, and sites specific examples (see page 409, first col.). Verma et al (Nature, 1997; Vol. 389) teaches, "there is still no single outcome that we can point to as a success story" (see pg. 239, col. 1; Gene Therapy Promises, Problems and Prospects). Furthermore, both Verma and Crystal teach that delivery of the therapeutic nucleic acid to the specific target cells is crucial, and indicate specific delivery of the therapeutic nucleic acid by systemic administration is still a formidable obstacle to overcome.

Regarding therapeutic gene targeting, Yanez et al. (Gene Therapy; Vol. 5, p. 149-159; 1998) teaches, "While gene targeting has been achieved both in human cell lines and in non-transformed primary human cells, its low efficiency has been a major limitation to its therapeutic potential. Gene therapy by in vivo gene targeting is therefore impractical without dramatic improvements in targeting efficiency. Ex vivo approaches might more realistically be considered, but would benefit from progress in the isolation and growth of somatic stem cells and improvements in targeting efficiency." (See abstract). Yanez also teaches that although reports that gene targeting using oligonucleotides have dramatically improved gene targeting frequencies, "Unfortunately, the logarithmic relationship between targeting efficiency and length

of homology suggests that simple nucleic acids with small regions of homology will not be sufficient." (See p.153, last paragraph). Regarding the reports that DNA-RNA hybrid oligonucleotides were able to correct a single base mutation of the β-globin gene in immortalized B cells from a patient with sickle cell anemia, Yanez remarks, "as has recently been pointed out, further controls are required to rule out the possibilities of screening artefacts and cell contamination. An unambiguous demonstration of targeted correction would involve the isolation of a clonal cell population bearing both a corrected β-globin allele (as judged by Southern analysis) and an otherwise patient-specific genotype (as judged e.g. by DNA-fingerprint analysis)." (See p. 154, first paragraph). Yanez states in the final remarks that, "Many old and new questions remain unanswered. We do not understand why different loci appear to target at different frequencies, and whether this may be related to epigenetic factors such as DNA methylation or chromatin condensation. It is unknown how the proteins of HR [homologous recombination] are recruited to the DSB [double strand break], and little is known about the decision making that drives DSB repair to NHR [non-homologous recombination] and HR" and, " In vivo gene therapy by gene targeting is not viable at present." (See p. 156, under Final Remarks).

More recently, regarding the use of oligonucleotides for targeted gene repair, Gamper et al. (Nucleic Acids Research; Vol. 28, No. 21:4332-4339; 2000) states that the frequency of repair "still represents only a 0.1%-0.2% conversion rate, we may be moving closer to direct applications of gene repair in vivo." (See p. 4338, last paragraph). Indicating that the efficiency of targeted repair still needs improvement. Furthermore, Culver et al. (Nature Biotech. Vol. 17:989-993; 1999) indicates that, "Further experiments with bifunctional oligonucleotides are

needed to optimize their structural design, fully characterize the limits on size of mutations that can be repaired, and determine the influences of the various components of the DNA repair complex on the efficiency of correction." (See p. 992, third paragraph).

The claims are also drawn to targeting of nucleic acids in stem cells which are contemplated as useful for stem cell therapy. Regarding stem cell therapy, Kaji et al. (JAMA, Vol. 285, No. 5:545-550; 2001) teaches, "Much additional work remains to be done in the areas of vector development and stem cell biology before the full therapeutic potential of these approaches can be realized. Of equal importance, the ethical issues surrounding gene- and cell-based therapies must be confronted." (See abstract, p. 545).

Working Examples and Guidance in the Specification

The specification has only two working example of using oligonucleotides for successful targeted alteration. One example disclosed is of successful alteration of a nucleic acid in yeast (Example 2, p. 32), while the other example indicates alteration of a target sequence in a cell-free extract. There are no working examples of successful gene making targeted genetic alterations in cells that are in vivo. There are a number of possible genetic disorders that are mentioned as candidates for gene targeting (see Examples 3-25), and the possibility of genetically altering plants using oligonucleotides is also mentioned (see Example 26); however, these examples (Examples 3-26) are only prophetic, and do not disclose the successful alteration of genetic material. Furthermore, there are no examples indicating that the method can be used successfully for stem cell therapy.

Quantity of Experimentation

Considering the breadth of the claims (i.e. encompassing genetic alteration in cells in vivo and stem cell therapy) as well as the problems that recognized in the art, the quantity of experimentation is extremely large since determination of the efficacy of targeted alteration of genetic material would require experimentation testing base addition, deletion and alteration in cells that are in vivo and also using altered stem cells for therapeutic purposes. Considering the problems recognized in the art, it is apparent that the experimentation required to overcome these problems is not routine. For example, after years of experimentation one of skill in the art cannot predictably deliver a nucleic acid of sequence to a specific cell/cells in vivo by systemic administration. Furthermore, after years of experimentation stem cell therapy is still no a routine.

Level of the skill in the art

The level of the skill in the art is deemed to be high.

Conclusion

Considering the high degree of unpredictability of gene therapy (including therapeutic gene targeting) recognized in the art, the breadth of the claims, the lack of working examples and guidance in the specification; and the high degree of skill required, it is concluded that the amount of experimentation required to perform the full scope of the broadly claimed method is undue.

Claim Rejections - 35 USC § 103

14. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various

claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

15. Claims 25-38, 40-58 and 63-69 rejected under 35 U.S.C. 103(a) as being obvious over Yamamoto et al. (Genetics 131:811-819; 1992, cited in IDS) in view of Meyer et al. (US Patent 6,136,601).

The applied reference (Meyer) has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the

same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

Yamamoto teaches a method for targeted sequence alteration of a nucleic acid sequence using a single stranded oligonucleotide that does not form hairpin structures and which is fully complementary to the target sequence except one or more mismatches that are centrally located in the oligonucleotide. Specifically, Yamamoto teaches that the single stranded oligonucleotide is in the range of 17-121 nucleotides long which do not appear and are not disclosed as capable of forming a hairpin (e.g., see p. 813 Table 1; p. 814, Table 2, etc.). The oligonucleotide comprises a domain of at least 8 contiguous deoxyribonucleotides (e.g. all of the nucleotides of Yamamoto may be deoxyribonucleotides). Yamamoto teaches that the oligonucleotide can be used to make site-directed genetic alteration of double stranded DNA in S. cerevisiae (a yeast cell) (e.g., see p. 811, abstract).

Yamamoto does not teach that the oligonucleotide comprises base modifications, such as 2-O-Me or phosphorothioates. Nor does Yamamoto teach that the oligonucleotide can be used to make site directed sequence modification in other cell types such as bacteria, or animal cells.

However, Meyer also teaches a method for targeted sequence alteration of a nucleic acid using a single stranded oligonucleotide that do not form hairpin structures and which can be used to make targeted genetic alterations in nucleic acids present within cells. Meyer teaches that the oligonucleotide can be comprised of modifications which decrease the oligonucleotides sensitivity to nuclease degradation, including 2-O-Me base analogs and phosphorothioate linkages (e.g., see col. 7, lines 29-60). An oligonucleotide comprising the 2-O-Me or phophorothioate modifications would necessarily comprise these modifications as terminal

modifications (e.g., see col. 7, lines 29-67). Meyer also teaches that the oligonucleotides can be used to make targeted genetic alterations in bacteria cells as well as animal cells, including human cells (e.g., see col. 14, lines 28-31). Furthermore, Meyer indicates that the oligonucleotide could be used to make genetic alterations in double stranded DNA that is present in chromosomes in cells such as plant, fungus, bacteria, etc.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to modify the oligonucleotide used by Yamamoto such that it comprised the base modifications 2-O-Me or phosphorothioates taught by Meyer, with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to make the alterations to the Yamamoto oligonucleotide because Meyer indicates that the 2-O-Me and phosphorothioate modifications are preferable modifications to have in oligonucleotides used for site directed alterations in cells. Furthermore, it would have been prima facie obvious that the oligonucleotide could have been used to target any double stranded nucleic acid sequence such as artificial chromosomes, episomal genomic DNA, or nucleic acids present in other mammalian cells such as rodent or monkey cells, as all of these potential target sequences would have been well known to one of skill of in the art based on the disclosure in the present specification.

16. Claims 25-30, 37, 38, 40, 44-47 and 53-62 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto et al. (Genetics 131:811-819; 1992, cited in IDS) in view of Wengel et al. (WO 99/14226, cited in IDS).

Yamamoto teaches a method for targeted sequence alteration of a nucleic acid sequence using a single stranded oligonucleotide that does not form hairpin structures and which is fully complementary to the target sequence except one or more mismatches that are centrally located in the oligonucleotide. Specifically, Yamamoto teaches that the single stranded oligonucleotide is in the range of 17-121 nucleotides long which do not appear and are not disclosed as capable of forming a hairpin (e.g., see p. 813 Table 1; p. 814, Table 2, etc.). The oligonucleotide comprises a domain of at least 8 contiguous deoxyribonucleotides (e.g. all of the nucleotides of Yamamoto may be deoxyribonucleotides). Yamamoto teaches that the oligonucleotide can be used to make site-directed genetic alteration of double stranded DNA in S. cerevisiae (a yeast cell) (e.g., see p. 811, abstract).

Yamamoto does not teach that the oligonucleotide comprises at least one terminal locked nucleic acid (LNA).

However, Wengel teaches nucleoside/nucleotide analogues known as locked nucleoside analogues (LNAs), and oligonucleotides comprising the analogues. Wengel indicates that LNAs improve the affinity and specificity of the oligonucleotide to its complementary sequence (e.g., see abstract. Wengel also teaches that the oligonucleotides can comprising 1-10000 LNAs and be effective.

Therefore, it would have been prima facie obvious to one of ordinary skill in the at the time of filing to modify the oligonucleotide taught by Yamamoto with the LNA modification taught by Wengel to make the claimed invention with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to make the modification to the targeting oligonucleotide because Wengel teaches that the LNA modification improves the

affinity and specificity of the oligonucleotide for its target sequence. Furthermore, it would have been a matter of routine optimization to one of skill in the art to identify the optimal number and location of LNAs for the oligonucleotide.

17. Claims 25-30, 37, 38, 40, 44-47, 53-58 and 63-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Yamamoto et al. (Genetics 131:811-819; 1992, cited in IDS) in view of Wengel et al. (WO 99/14226, cited in IDS).

Yamamoto teaches a method for targeted sequence alteration of a nucleic acid sequence using a single stranded oligonucleotide that does not form hairpin structures and which is fully complementary to the target sequence except one or more mismatches that are centrally located in the oligonucleotide. Specifically, Yamamoto teaches that the single stranded oligonucleotide is in the range of 17-121 nucleotides long which do not appear and are not disclosed as capable of forming a hairpin (e.g., see p. 813 Table 1; p. 814, Table 2, etc.). The oligonucleotide comprises a domain of at least 8 contiguous deoxyribonucleotides (e.g. all of the nucleotides of Yamamoto may be deoxyribonucleotides). Yamamoto teaches that the oligonucleotide can be used to make site-directed genetic alteration of double stranded DNA in S. cerevisiae (a yeast cell) (e.g., see p. 811, abstract).

Yamamoto does not teach that the oligonucleotide comprises at least one 2-O-Me or phosphorothioates.

However, Barracchini teaches therapeutic oligonucleotides comprising 2-O-Me or phosphorothioate modifications. Barrachini teaches that therapeutic oligonucleotides comprising 2-O-Me or phosphorothioate modifications are preferable over native forms because of desirable

properties such as, for example, enhanced cellular uptake, enhanced affinity for the target nucleic acid sequence, and increased stability in the presence of nucleases (e.g., see col. 6, lines 25 through col. 7, line 14).

Therefore, it would have been prima facie obvious to one of ordinary skill in the at the time of filing to modify the oligonucleotide taught by Yamamoto with the 2-O-Me or phophorothioate modification taught by Barrachini to make the claimed invention with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to make the modification to the targeting oligonucleotide because Barrachini teaches that the 2-O-Me and phophorothioate modifications may enhance cellular uptake, enhance affinity for the target nucleic acid sequence, and/or increase stability in the presence of nucleases (e.g., see col. 6, lines 25 through col. 7, line 14). Furthermore, it would have been a matter of routine optimization to one of skill in the art to identify the optimal number and locations of the modifications for the oligonucleotide.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for

the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

DAVE T. NGUYEN
PRIMARY EXAMINER

J. Eric Angell
May 19, 2003